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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,17,22 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 13, 17, 22, 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments to the claims filed July 7, 2008 have been entered. Claims 1-11, 14-16, 18-21, 23-49 have been canceled, while claims 13, 17, 22, 50-52 and 53 have been amended.

Claims 12, 13, 17, 22, 50-53 are pending and currently under examination.

Election/Restrictions

Applicant's response to the Restriction was received on 12/20/2004. Applicants elected the subject matter of group I, drawn to a method of forming cells of the T cell lineage. Claims 18-21, 23, and 25-28 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-17, 22 and 24 were examined, while the examiner in the interests of compact prosecution rejoined claim 22.

Withdrawn-Claim Objections

The objection to claims 13, 17, 50-53 is withdrawn in view of amendments to the claims. Applicants have amended claims the recitation of "a method as claimed in .." to "The method of claim".

Withdrawn-Claim Rejections - 35 USC § 112

Claims 22, 52 and 53 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims. Applicants have amended claims to include the specific recitation of mature or immature T cell lineage cells showing fold increase in number as compared to method step that defines the reference to which cells are compared on the co-culture.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13, 17, 22, 50-53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al (1994, Science 265:5175 IDS), Pui et al (Immunity. 1999, 11(3):299-308) and Tatsumi et al (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS).

Applicants' arguments filed on July 7, 2008 have been fully considered but are not fully persuasive.

As an initial matter it is noted that claims are directed to methods that require one active step of culturing any stem or progenitor cells with a cell preparation comprising OP-9 stromal cell that have been modified to express Delta like -1 or Delta Like-4. It is emphasized that recitation of forming T cell (claim 19) or isolating increased number is resulting effect that is inherent in culturing stem cell on stromal cell modified to express Dl1 or DL-4.

Applicants argue on two grounds (i) none of the reference teaches T cell linage development (ii) use of notch and not notch ligand DL-1 or DL-4 (see page 6 of the arguments). Applicants also argue about hindsight selection of which ligand DL-1 and/or DL-4 would be sufficient in any stromal cell line. Applicants assert that if OP-9 was functionally equivalent to SL-17 then SL17 should also have produced

claimed T cell lineage cell (see page 7). Applicants also argues that there must be some suggestion in prior art to combine the cited references. Regarding teaching of T cell linage development and use of notch and not notch ligand, it is noted that it is Jaleco et al. and not the secondary reference that provides guidance on a method of using an *in vitro* system comprising stromal cells that is modified to express Delta-1 ligand, does not support B cell lymphopoiesis (Abstract). Examiner would agree that Jaleco did not explicitly disclose support of TCR-γδ+T cell , however, he clearly teaches culturing HPCs with mouse S-17 stromal cells that express Delta-1 inhibits B cell differentiation and produces CD3+ CD4+CD8+ T cells (pg. 992, Materials and Methods; pg. 995, Table 1). Jaleco et al. also teach separating CD4+CD8+ T cells from the aggregate population of cells (pg. 995, Table 1). Thus double positive T cell produced by the system disclosed by Jaleco clearly meet a system that supports T-lymphopoiesis in which a population of T-cells is produced from precursor cells.

Although Jaleco taught a method to produce T cell linage comprising culturing stem cell that are capable of differentiating into T cell linage with a cell preparation comprising stromal cell (SL-17) that have been modified to express notch ligand that support T cell lymphopoiesis, but differed from claimed invention by not disclosing modifying any other stromal cell including OP-9 with DL-1.

The reference of Nakano et al. is supplied to demonstrate that stromal cells such as ST2, PA6 and RPO.10 were examined to study co culture of ES cells on stromal cell without exogenous growth factor (see page 1098, col. 2. para. 1). Thus, use of several different stromal cell lines in culture of stem cells is known in the art. Nakano et al. provide motivation to use OP9 cells in particular, which lacks M-CSF, when studying lymphopoiesis because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages.

With respect to applicants' argument that OP-9 is not functionally equivalent to SL-17, it is noted that Applicants have previously agreed that Jaleco et al teaches that culturing human progenitor cells with mouse S-17 stromal cells that

express Delta-1 (S-17-DL1) produces low levels of CD3+ CD4+ CD8+ T-lineage cells (see page 5, last para.). This supports the Examiner's argument that co culturing progenitor cells with stromal cell that is modified to express DL-1 to study T-lineage cells was known in prior art. Furthermore, Jaleco et al clearly suggested that the results were obtained in a short time culture assay (when $CD34^{+/}$ cells have not yet acquired any T cell marker), a possibility is that up regulation of pre-Tα expression may occur at later time points of culture, when cells have reached a more advanced developmental stage (See page 999, col. 1, last para to col. 2). Applicants' argument of Pui et al not disclosing modifying OP-9 with any specific Notch ligand is not persuasive as this limitation is taught by Jaleco. Tatsumi supplements the guidance of Jaleco et al. by teaching an *in vitro* system for studying the differentiation of immature double negative T cells into more mature mouse T cells from by co culturing them with mouse stromal cells (Abstract; pg. 2750, Materials and Methods).

Applicants' argument of showing that expression of DL-1 or DL-4 in NIH3T3 cells is insufficient to support T-cell development (citing Mohtashami and Zuniga-Pflucker) is irrelevant as claims are directed to co culturing stem cells with stromal cells that is modified to express DL-1. It is emphasized that fibroblast cells are not stromal cells. The rejection is applied to substituting one stromal cells with another in the method disclosed by Jaleco.

With respect to applicant's argument that there is nothing in art that would motivate the substitution of one stromal cell (SL-17) with another (OP-9), it is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of

disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant's contribution to the art is simply to claim co culturing stem or progenitor cells on another stromal cell (OP9) that is modified to express DL-1 or DL-4 obvious, but not specifically obvious, to the Artisan at the time of invention as KSR has already stated that motivation need not be specific, and only in the case of an infinite number of variants is a specific variant non-obvious. Use of multiple different stromal cell lines in coculture of stem or progenitor cells was clearly known in the art. Nakano provided motivation to use OP9 stromal cells in particular, given desirable advantages that were well-known and accepted at the time of filing. Given that one of ordinary skill in the art was well aware that OP-9 stromal cells derived from macrophage colony-stimulating factor (M-CSF)-deficient osteopetrotic mice lacks M-CSF and could inhibit the differentiation of ES cells to blood cells other than macrophages while studying lymphopoiesis, the requirements for modifying stromal cell to express Notch ligand DL-1, as in Jaleco, and was already able to produce cells of T cell linage by culturing stem cell on another stromal cell (SL-17) that is modified to express Dl-1. Hence, it is prima facie obvious to one the artisan to modify the method of Jaleco by substituting one stromal cell (SL-17) with another OP-9 that is modified to express DL-1 with reasonable expectation of successfully achieving predictable result. Additionally, formation of cells of T cell linage would be implicit effect of culturing stem cell with a stromal cell (OP-9) that is modified to express a Notch ligand DL-1, particularly since Jaleco et al embraced the idea of up regulation of pre-Tα expression at later time points of culture, when cells have reached a more advanced developmental stage.

Applicants have previously argued regarding comparative data provided in the example 9 of the instant application, it is was noted that data shows under similar condition both stromal layer are capable of producing B cells with equal efficiency from HPCs cultured on control OP9-GFP or S17-GFP cells. However,

there was a marked difference in the generation of T cells on S17-DL1 cells (5% DP cells) as compared to OP9-DL1 cells (65% DP cells). In the instant case, the claimed method is directed to a method of forming cells of T cell lineage, irrespective of efficiency of the system. The evidence provided in the specification teaches better efficiency of producing cell of T cell lineage on OP-9; however, it does not preclude generation of T cells on S17-DL1 as suggested by Jaleco for loner duration of culture. Applicants have neither rebutted nor provided evidence to demonstrate that condition that produces T cells of different lineage (cell type, incubation time, growth medium and other condition) on OP9-DL1 would not be produced under similar cells on S17-DL1. It is emphasized that method of forming T cell on another stromal cell may be of varying efficiency; however, its production under similar condition is not unexpected. MPEP 2145 states "If a prima facie case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case. See, e.g., In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented in the specification, or by way of an affidavit or declaration under 37 CFR 1.132, e.g., Soni, 54 F.3d at 750, 34 USPQ2d at 1687; In re Piasecki, 745 F.2d 1468, 1474, 223 USPQ 785, 789-90 (Fed. Cir. 1984). In absence of any objective evidence or declaration the rejection of record is maintained.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pykett et al US Patent No. 7067316, dated 6/27/2006, effective filing date 9/25/1998).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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